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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,682	05/16/2001	Ning Li	031855.0007	1553

26118 7590 02/28/2003

BROBECK, PHLEGER & HARRISON, LLP
ATTN: INTELLECTUAL PROPERTY DEPARTMENT
1333 H STREET, N.W. SUITE 800
WASHINGTON, DC 20005

EXAMINER

EINSMANN, JULIET CAROLINE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 02/28/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/855,682

Applicant(s)

LI ET AL.

Examiner

Juliet C Einsmann

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 7-9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

Art Unit: 1634

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 12/5/02, paper number 18. Claims 1 and 2 have been amended and claims 3-10 have been added. Claims 1-10 are pending, and are subject to restriction as set forth herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Priority

2. Applicant's amendment to the first line of the specification indicating a claim to priority to parent application 09/239796 is noted. In light of this amendment, and in light of the amendments to the claims, new grounds of rejection are set forth herein.

Sequence Rules

3. The application is in compliance with the sequence rules.

Election/Restrictions

4. Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-6 and 10, drawn to methods for screening pigs to determine those more likely to produce larger litters, classified in class 435, subclass 6.
- II. Claims 7-9, drawn to kits comprising reagents which identify a genetic polymorphism, classified in class 536, subclass 24.3.

Art Unit: 1634

The inventions are distinct, each from the other because of the following reasons:

5. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kits of invention II can be used in a variety of methods including nucleic acid amplification, the study of other aspects of porcine reproductive physiology, aptamer methods, and nucleic acid purification methods.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-II require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

7. Newly submitted claims 7-9 are directed to an invention that is independent or distinct from the invention originally claimed for the stated reasons.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 7-9 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1634

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-6 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 are indefinite over the recitation “at least one marker linked to the FSH β -subunit allele(s) of SEQ ID NO: 1” because it is not clear what applicant intends to be referring to as an allele of SEQ ID NO: 1. The specification disclosed that SEQ ID NO: 1 is a retroposon whose presence within the gene encoding FSH β -subunit in a pig is associated with smaller litter size. Thus, one allele of the FSH β -subunit gene is when SEQ ID NO: 1 is present and one allele of the FSH β -subunit gene is when SEQ ID NO: 1 is absent. It is not clear what applicant intends when referring to alleles of SEQ ID NO: 1 itself, because this language appears to refer to variability within SEQ ID NO: 1, but in light of the specification, it is not clear that applicant has ever contemplated such variability. Thus, the claims are indefinite because the phrase “the FSH β -subunit allele(s) of SEQ ID NO: 1” lacks proper antecedent basis in the claims and the specification because neither previously refer to alleles of SEQ ID NO: 1.

Claim 10 is indefinite because it depends from non-elected claim 9, and thus the metes and bounds of claim 10 are unclear because the claim is effectively incomplete.

Claim Rejections - 35 USC § 112

10. Claims 1-6 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of screening to detect the specific insertion of a retroposin comprising SEQ ID NO: 1 in the FSH β -subunit gene, does not reasonably provide

Art Unit: 1634

enablement for detection of any additional alleles of the FSH β -subunit. Furthermore, the specification and prior art, while being enabling for the detection of the ESR gene and the OPN gene as genes that are associated with pig litter size do not provide enablement for the detection of additional genes associated with pig litter size. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The invention relates to methods for screening pigs to determine those more likely to produce larger litters and/or those less likely to produce larger litters. The method steps of claims 1 and 2 require determining the presence of at least one marker linked to the FSH β -subunit allele(s) of SEQ ID NO: 1. Thus, the scope of claims 1 and 2 includes using any marker linked to instant SEQ ID NO: 1 as an indicator that a pig is more or less likely to produce a larger litter. The method steps of claims 3-6 and 10 require determining the presence of at least one FSH β -subunit allele associated with pig litter size, and the determining the presence of one other gene associated with pig litter size. Claims 5 and 6 limit the scope of the "other gene" to the ESR gene or the OPN gene. The scope of claims 3-6 and 10 includes using any marker within the FSH β -subunit gene as an indicator that a pig is more or less likely to produce a larger

Art Unit: 1634

litter, and further, claims 3-4 and 10 encompass the detection of any possible second gene that is associated with pig litter size.

The specification contains a single working example, demonstrating that a specific inserted retroposon allele is linked was linked to litter size. Namely, the specification demonstrates that when SEQ ID NO: 1 is present in the FSH β -subunit gene of a female pig, that pig is more likely to produce a smaller litter than when SEQ ID NO: 1 is absent in the FSH β -subunit gene of the pig (See Examples 1 and 2). The specification further speculates that it is also possible to establish linkage between specific alleles of "alternative DNA markers" and the FSH β -subunit allele disclosed in the instant specification. There is not specific teaching in the specification regarding these alternative markers, besides the speculation that they may exist.

With regard to the "other genes" recited in claims 3-6 and 10, the specification teaches that the prior art provides disclosure that the OPN and ESR genes have previously been shown to be associated with pig litter size. The specification does not disclose or suggest any additional genes that might be associated with pig litter size.

The prior art includes the disclosure of an eleven base pair deletion from the FSH β -subunit which is present only in Chinese Meishan pigs (Li *et al.* Biology of Reproduction, August 1997, Volume 56, Supp. p. 119, abstract #148). (Meishan pigs are known for their prolificacy.) The prior art also discloses one other RFLP which is the result of a point mutation, but no association between this mutation and pig litter size (Rohrer *et al.* Mammalian Genome, 5, 315-317 (1994)). Thus, the prior art includes the teaching of two other possible genetic variants in the FSH β -subunit, but there is not other teaching of FSH β -subunit variants in the

Art Unit: 1634

prior art, nor is there clear evidence that any polymorphism found within the FSH β -subunit gene or any other "linked" gene would necessarily be linked to increased litter size. With regard to the "other" gene recited in claims 3-6 and 10, teaches a single polymorphism present in the OPN gene that is associated with pig litter size (WO 96/41892) and a single polymorphism present in the ESR gene that is associated with pig litter size (WO 92/18651).

In order to practice the claimed method commensurate with its full scope, a practitioner would be required to identify additional polymorphisms within and linked to the FSH β -subunit gene that are predictive of litter size in pigs. Further, a practitioner would be required to identify additional genes that are associated with pig litter size. The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. The amount of direction or guidance presented in the specification and the prior art of only three different FSH β -subunit polymorphisms compared to any pig FSH β -subunit polymorphic sequence is minimal, given that just the redundancy of the genetic code of the approximately 100 amino acid protein would allow for several thousand different sequences while when conserved or non-conserved mutations are considered, millions of different sequences for the pig FSH β -subunit may exist which may, or may not, have substantial functional differences. Furthermore, claims 1 and 2 encompass the use of markers that are not even within the FSH β -subunit gene, as to the remaining claims which require the detection of an additional gene associated with pig litter size. There are no working examples of additional sequences other than those disclosed in either the specification or the prior art. The post-filing date art of Linville *et al.* exemplify the unpredictability in this area of technology. Linville *et al.* attempted to demonstrate a correlation

Art Unit: 1634

between a alleles in five different candidate genes and pig litter size, but were unable to do so (see abstract and results). Notably, one of these alleles was a restriction allele in allele of the FSH β -subunit gene (see Table 1). Linville *et al.* note that a previous study had demonstrated an association between an allele within the FSH β -subunit gene and pig litter size, teach that the polymorphism they studied may be in less linkage disequilibrium with the causative mutation. Thus, even within the FSH β -subunit gene, it is highly unpredictable as to whether or not a given polymorphism will be associated with pig litter size.

Although the level of skill in the art of nucleic acid analysis is high (the Ph.D. degree with laboratory experience), there is no predictability for which sequences exist which code for polymorphisms in pig FSH β -subunit genes. The quantity of experimentation that would be necessary to determine even one additional polymorphism in the pig FSH β -subunit gene is substantial. Applicants have not disclosed how one would go about detecting such polymorphisms that would be necessary to practice the claimed invention. Because there is no reason to expect that any additional polymorphism is associated with litter size and because of the very large number of possible polymorphisms, screening for additional polymorphisms that would be indicators or increased litter size would require performing and screening many, many successful breedings of pigs. There is no evidence, however, of any frequency of significant polymorphisms. Further, even in positive matches, the FSH β -subunit polymorphism may not correlate with litter size, as was found by Linville *et al.* The FSH β -subunit polymorphism may be coincident and unrelated with a different, unlinked (on the chromosome) polymorphism such as an FSH α -subunit polymorphism or a polymorphism in an undetermined gene that actually

Art Unit: 1634

regulates litter size. The FSH β -subunit polymorphism would not have any meaning or effect, but might appear to influence litter size due to its close proximity to some other gene. The extreme unpredictability of polymorphisms in the art, combined with the absence of teaching in the prior and the large quantity of experimentation necessary in the art support a conclusion that undue experimentation is required to make and use the invention as broadly claimed.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention relates to methods for screening pigs to determine those more likely to produce larger litters and/or those less likely to produce larger litters. The method steps of claims 1 and 2 require determining the presence of at least one marker linked to the FSH β -subunit allele(s) of SEQ ID NO: 1. Thus, the scope of claims 1 and 2 includes using any marker linked to instant SEQ ID NO: 1 as an indicator that a pig is more or less likely to produce a larger litter. The method steps of claims 3-6 and 10 require determining the presence of at least one FSH β -subunit allele associated with pig litter size, and the determining the presence of one

Art Unit: 1634

other gene associated with pig litter size. Claims 5 and 6 limit the scope of the “other gene” to the ESR gene or the OPN gene. The scope of claims 3-6 and 10 includes using any marker within the FSH β -subunit gene as an indicator that a pig is more or less likely to produce a larger litter, and further, claims 3-4 and 10 encompass the detection of any possible second gene that is associated with pig litter size.

The specification contains a single working example, demonstrating that a specific inserted retroposon allele is linked was linked to litter size. Namely, the specification demonstrates that when SEQ ID NO: 1 is present in the FSH β -subunit gene of a female pig, that pig is more likely to produce a smaller litter than when SEQ ID NO: 1 is absent in the FSH β -subunit gene of the pig (See Examples 1 and 2). The specification further speculates that it is also possible to establish linkage between specific alleles of “alternative DNA markers” and the FSH β -subunit allele disclosed in the instant specification. There is not specific teaching in the specification regarding these alternative markers, besides the speculation that they may exist. Thus, the genus of polymorphisms required to practice the claimed inventions includes any possible additional polymorphisms within the FSH β -subunit gene that is associated with pig litter size or linked to the disclosed polymorphism, or and additional “other” gene associated with pig litter size Thus, applicant has express possession of only one species in a genus which comprises at least hundreds of different possibilities.

With regard to the written description, all of these claims encompass the use of different polymorphisms from those disclosed in the specification.

Art Unit: 1634

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

"...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only the specific structure of a single polymorphism has been disclosed. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of methods which utilize any polymorphism other than the single retroposon described in the specification.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Art Unit: 1634

13. Claims 1-6 and 10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6291174. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '174 patent are a species of claims 1-2 and thus anticipate the claim. With regard to claims 3-6 and 10, these claims differ from the claims of the '174 patent because they recite the examination of an additional gene. However, the '174 patent discloses this as a preferred embodiment within the portion of the specification that supports claims 1-3 of the '174 patent. Therefore, it would have been prima facie obvious in view of the '174 patent to examine an additional gene because this is a preferred embodiment within the patent.

Response to Remarks

The rejections have all been modified in light of applicant's amendments. Applicant's remarks are addressed insofar as they are relevant to the pending claims.

Applicants assert in the last paragraph of page 7 that ample evidence exists in the specification as filed to demonstrate that applicants were in possession of the claimed invention. Applicants point to page 3 of the specification to support the assertion that they were in possession of additional markers of litter size that would be linked to instant SEQ ID NO: 1. However, this prophetic statement does not indicate possession of the additional markers necessary to practice the claimed invention. While it is noted that applicants are not claiming a specific DNA sequence, the knowledge of these specific DNA markers is necessary for the practice of the claimed invention. Applicant refers to the post filing date art of Slatkin *et al.* for a

Art Unit: 1634

general statement that markers in strong linkage disequilibrium with a disease phenotype are likely to be linked to the causative locus. However, this is not a statement that the actual markers are known by applicant or in applicant's possession. That such additional markers even exist within or near the FSH β -subunit gene is unknown at the time of filing. When Linville *et al.* were unable to detect associations between genes and litter size in particular, they stated

“One possible reason for the lack of effect in the current study, by genes that had positive effects on litter size in other studies, is that different linkage disequilibrium existed in the populations. The polymorphisms in the genes studied may not directly affect the trait. These polymorphisms could be markers linked with the causative mutation within the gene or a closely linked gene (p. 66).”

Again, however, these linked markers are unknown and unpredictable. The postulation that additional markers exist does not demonstrate possession of the markers or provide description of them for use in the claimed methods.

With regard to the written description rejection, applicant further argues that once a polymorphism is found it would be routine to associate it with the trait. This is not persuasive for the written description rejection because it does not address the issue at hand, which is that the additional polymorphisms associated with the trait are undisclosed entirely. Further, court has made it clear that with regard to chemical compounds, the standard for written description is possession, not enablement or intent to claim. “While we have no doubt a person so motivated would be enabled by the specification to make it, this is beside the point for the question is not whether he would be so enabled but whether the specification discloses the compound to him, specifically, as something appellants actually invented. We think it does not.” In Re Ruschig, 379 F.2d 990, 995, 154 U.S.P.Q. 118, 123 (CCPA 1967). Furthermore, the court stated

Art Unit: 1634

“Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.” The Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q.2d 1406 (Federal Circuit 1997). In the instant case, although applicant has provided a general function (association with litter size) this are not sufficient to convey possession of the entire possible group of methods for identifying pigs that are encompassed by the instant claims.

Conclusion

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Art Unit: 1634

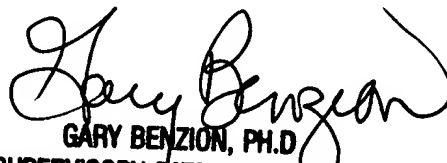
16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Juliet C. Einsmann can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Einsmann
Examiner
Art Unit 1634

February 22, 2003


GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600